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ELSEVIER FULL-TEXT ARTICLE

NMDA receptor subunits in the postsynaptic density of rat brain expression and phosphorylation by endogenous protein kinases.

Suen PC, Wu K, Xu JL, Lin SY, Levine ES, Black IB.

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N-methyl-D-aspartate (NMDA) receptors (NRs) play critical roles in diverse synaptic processes in the brain. However, subcellular distribution, spatiotempor expression and regulation of NR subunits in brain synapses are unknown. We report that NR1 and NR2A-2C subunits are all enriched in the postsynaptic density (PSD), which plays critical roles in trophin-mediated synaptic plasticity Significant expression of NRs was observed the first two weeks after birth, duri synaptogenesis, and in adulthood. Functional diversity of NRs, resulting from heterogeneous composition, was supported by the finding that different NR2 subunits were associated in a region-specific manner with NR1. Phosphorylatio of NR1, a key subunit of the NMDA receptor-channel complex, was significant enhanced by activators of calmodulin (CaM) kinases (CKs) or protein kinase C (PKC), but not by those of PKA. Co-immunoprecipitation studies revealed that NR1 was physically associated with functionally active PKCgamma and the ma PSD protein (mPSDp) through noncovalent interactions. Our results suggest tha NMDA receptors play roles in postsynaptic mechanisms in a subunit-, composition-, brain region- and developmental-specific manner. Our findings a indicate that the PSD is a coherent functional unit containing protein kinases th potentially regulate NMDA receptor function via phosphorylation.

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Biochemical studies of the structure and function of the N-methyl-D-aspartate subtype of glutamate receptors.

Dunah AW, Yasuda RP, Luo J, Wang Y, Prybylowski KL, Wolfe BB.

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The N-methyl-D-aspartate (NMDA) subtype of glutamate receptors plays a key role in synaptic transmission, synaptic plasticity, synaptogenesis, and excitotoxicity in the mammalian central nervous system. The NMDA receptor channel is formed from two gene products from two glutamate receptor subunit families, termed NR1 and NR2. Although the subunit composition of native NMDA receptors is incompletely understood, electrophysiological studies using recombinant receptors suggest that functional NMDA receptors consist of heteromers containing combinations of NR1, which is essential for channel activity, and NR2, which modulates the properties of the channels. The lack of agonists or antagonists selective for a given subunit of NMDA receptors has ma it difficult to understand the subunit expression, subunit composition, and posttranslational modification mechanisms of native NMDA receptors. Therefo most studies on NMDA receptors that examine regional expression and ontoger have been focused at the level of the mRNAs encoding the different subunits using northern blotting, ribonuclease protection, and in situ hybridization techniques. However, the data from these studies do not provide clear informati about the resultant subunit protein. To directly examine the protein product of tl NMDA receptor subunit genes, the development of subunit-specific antibodies using peptides and fusion proteins has provided a good approach for localizing, quantifying, and characterizing the receptor subunits in tissues and transfected c lines, and to study the subunit composition and the functional effects of posttranslational processing of the NMDA subunits, particularly the phosphorylation profiles of NMDA glutamate receptors.

Publication Types:

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ELSEVIER FULL-TEXT ARTICLE

Altered expression and phosphorylation of N-methyl-D-aspartat receptors in piglet striatum after hypoxia-ischemia.

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The mechanisms for the profound degeneration of striatal neurons after hypoxia-ischemia in newborns are not understood. We hypothesized that this striatal neurodegeneration is related to N-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity. Using a 1-week-old piglet model of hypoxia-ischemia, we evaluated whether the expression and phosphorylation of NMDA receptor subunits in striatum are modified with severity of evolving neuronal injury after hypoxia-ischemia. Protein levels of NR1, phosphorylated NR1 897serine, NR2A and NR2B in striatum were measured by immunoblottin after piglets underwent hypoxic-asphyxic cardiac arrest, cardiopulmonary resuscitation, and recovery for 3, 6, 12 or 24 h. In membrane fractions isolated from total striatum, mean NR1 and NR2A levels did not change significantly w time after hypoxia-ischemia compared to control; however, the levels of both N and phosphorylated NR1 897serine correlated with neuronal injury in putamen, with higher levels associated with greater neuronal injury in individual animals. NR2B levels were increased at 24 h after hypoxia-ischemia. Astrocyte expressi of NR2B was prominent after hypoxia-ischemia. We conclude that NMDA receptors are changed in striatum after neonatal hypoxia-ischemia and that abnormal NMDA receptor potentiation through increased NR1 phosphorylation may participate in the mechanisms of striatal neuron degeneration after hypoxia-ischemia.

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ELSEVIER FULL-TEXT ARTICLE

An ER retention signal explains differences in surface expressior of NMDA and AMPA receptor subunits.

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The molecular mechanisms that control the surface expression of NMDA receptors (NMDARs) and AMPA receptors (AMPARs) are unknown. To determine the role of the intracellular C-terminal tails of glutamate receptor subunits in the synaptic targeting of AMPARs and NMDARs, we fused the tails of the AMPAR subunits, GluR1 and GluR2, and the NMDAR subunit, NR1, to the human T lymphocyte membrane protein CD8 and expressed these construct in HEK293 cells and cultured hippocampal neurons. The GluR1 and GluR2 fusion proteins exhibited robust surface expression in the plasma membrane of neurons at synapses as did CD8 alone. In contrast, the NR1 fusion protein was retained intracellularly in both HEK293 cells and neurons because of the presen of an ER retention signal in the C1 cassette. This ER retention signal was overridden either by the addition of a PDZ domain-binding motif or by mimicki phosphorylation at a site adjacent to the retention signal. These results provide further evidence that the intracellular trafficking of AMPAR and NMDAR subunits are regulated independently at least in part because of differences in th protein-protein interactions of their intracellular C-terminal tails.

PMID: 11640925 [PubMed - indexed for MEDLINE]